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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/691,157	10/22/2003	Istvan Boldogh	265.00440101	6536

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MUETING, RAASCH & GEBHARDT, P.A.
P.O. BOX 581415
MINNEAPOLIS, MN 55458

EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 06/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/691,157	BOLDOGH ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-7 and SEQ ID NO:8 in the response filed April 29, 2005 is acknowledged. The traversal is on the ground(s) that the claimed inventions can be readily evaluated in one search without placing undue burden on the Examiner; in particular, the claims of issued patent 6,500,798 (a parent of the instant application) are drawn to SEQ ID NO:1-34, the Patent Office has already performed the search of SEQ ID NO:1-34, it does not place an undue burden on Examiner. The response has been considered, however, the argument is not found persuasive because the traversal is not on the grounds that the inventions are not independent and distinct, rather, the traversal is on the grounds that there is no burden of search. As such restriction is proper if two or more claimed inventions are either independent **or** distinct. See MPEP 803. Furthermore, coexamination of each of the additional groups and sequences would require search of subjects and sequences unnecessary for the examination of the elected claims. Even the parent application has searched all 34 sequences, the instant application, which claimed the subject matter distinct from the parent application, still requires search on the subject and sequences, thus, if all 34 sequences were included, it would require additional sequence search besides SEQ ID NO:8. Each sequence would be searched on at least 5 databases, therefore, a total of 34 x 5 =170 sets of search results need to be reviewed. Therefore, coexamination of each of these inventions would require a serious additional burden of search.

The restriction groups have acquired a separate status in the art as a separate subject for inventive effect and require independent searches. The search for each of the invention is not

coextensive particularly with regard to the literature search. A reference which would anticipate the invention of one group would not necessarily anticipate or make obvious any of the other group. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Burden in examining materially different groups having materially different issues also exist.

Upon reconsideration, SEQ ID NOs: 1-7 are included in Group I, thus claims 1-7 and SEQ ID NOs: 1-8 are examined.

The requirement is still deemed proper and is therefore made FINAL.

2. The pending applications, 09/641,801 and 09/641,802 submitted March 4, 2004, as part of information disclosure statement have been considered.

Informalities

The disclosure is objected to because of the following informalities:

3. At page 12, line 24, the text contains a web site identified by a URL, which is not permissible in the patent application and requires deletion. Appropriate correction is required.

Claim Objections

4. Claims 6 and 7 are objected to because the claim contains recitation of non-elected sequences (SEQ ID NOs: 9-34).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-5 and 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of modulating an intracellular signaling molecule in a cell, the method comprising contacting the cell with a modulator selected from the group of colostrinin, a constituent peptide of colostrinin with a defined sequence (e.g., SEQ ID NOs:1-8), or a combination thereof, wherein the modulator reduces 4HNE-protein adduct formation, inhibits 4HNE-mediated glutathione depletion, inhibits 4HNE-mediated activation of p53 protein and/or inhibits 4HNE-induced activation of c-Jun N-terminal kinases, does not reasonably provide enablement for a method of modulating an intracellular signaling molecule in a cell, the method comprising contacting the cell with a modulator selected from the group of a constituent peptide of colostrinin, an active analog thereof, and combinations thereof, where the structure of the constituent peptide or the active analog is not defined; or a method of down regulating 4HNE-mediated lipid peroxidation in a cell, the method comprising contacting the cell with a modulator selected from the group of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-5 and 7 encompass a method of modulating an intracellular signaling molecule or down regulating 4HNE-mediated lipid peroxidation in a cell, the method comprising contacting the cell with a modulator selected from the group of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof. The specification, however, only discloses cursory conclusions (page 2-4), which state that the present invention provides a method of modulating an intracellular signaling molecule or down regulating 4HNE-mediated

lipid peroxidation in a cell, comprising contacting the cell with colostrinin, a constituent peptide, an active analog or combinations thereof, where the active analog is an active analog of a constitute peptide of colostrinin selected from the group of SEQ ID NO:1-34, and the active analog comprises a peptide having an amino acid sequence with at least about 15% proline and having at least 70 % structural similarity to one or more constituent peptides of colostrinin. There are no indicia that the present application enables the full scope in view of the use of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof in the claimed method as discussed in the stated rejection. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the absence or presence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the constituent peptides of colostrinin, and the active analogs thereof, which are not adequately described or demonstrated in the specification.

(2). The presence of absence of working examples:

The specification has shown colostrinin reduces 4HNE-protein adduct formation in PC 12 cells (Example 1); colostrinin affects the oxidative metabolism in PC 12 cells (Example 2); Effects of colostrinin on 4HNE-induced loss of intracellur GSH levels (Example 3); 4HNE-induced activation of JNK is suppressed by colostrinin (Example 4); and colostrinin inhibits

4HNE-induced activation of p53 (Example 5). However, there are no working examples indicating 4HNE-mediated lipid peroxidation is down regulated by colostrinin, constituent peptides thereof or the active analogs thereof in a cell, nor demonstrating a method of modulating an intracellular signaling molecule in a cell using various constituent peptides or various active analogs thereof.

(3). The state of the prior art and relative skill of those in the art:

The related art indicates colostrinin and its fragment are useful for treating disorders of central nervous system, neurological disorders and neurodegenerative disorders and a composition comprising colostrinin or its constituent peptide is prepared (page 1, lines 29-page 2, line 5 of the instant application; WO 98/14473), and considerable evidence has indicated increased oxidative stress may play a role in the pathogenesis of neuron degeneration and death in the neurodegenerative disorders (Markesbery, Free Radical Biology & medicine 23, 134-147 (1997)). However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the use of various constituent peptides and active analogs thereof in the claimed method to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass a method of modulating an intracellular signaling molecule or down regulating 4HNE-mediated lipid peroxidation in a cell, the method comprising contacting the cell with a modulator selected from the group of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof. However, the specification has not provided sufficient teaching on identifying the active analogs for various constituent peptides of

colostrinin, and the use of colostrinin, its constituent peptide, or an active analog thereof in the method of down regulating 4HNE-mediated lipid peroxidation in a cell. Since the structures of constituent peptides and the active analogs are not specifically defined in the claimed method, it is unpredictable regarding the effects of these modulators.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of modulating an intracellular signaling molecule or down regulating 4HNE-mediated lipid peroxidation in a cell, the method comprising contacting the cell with a modulator selected from the group of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof. While the specification shows colostrinin reduces 4HNE-protein adduct formation in PC 12 cells (Example 1); colostrinin affects the oxidative metabolism in PC 12 cells (Example 2); Effects of colostrinin on 4HNE-induced loss of intracellur GSH levels (Example 3); 4HNE-induced activation of JNK is suppressed by colostrinin (Example 4); and colostrinin inhibits 4HNE-induced activation of p53 (Example 5), the specification does not show 4HNE-mediated lipid peroxidation is down regulated by colostrinin, constituent peptides thereof or the active analogs thereof in a cell, nor demonstrates the use of various constituent peptides or various active analogs thereof in the method of modulating an intracellular signaling molecule. Furthermore, there are no examples indicating the use of various constituent peptides of colostrinin or active analogs thereof in the claimed method. Since the specification does not provide sufficient teachings on the identities of various analogs and the effects of various constituent peptides and their analogs in the claimed methods,

it is necessary to carry out undue experimentation to identify the active constituent peptides and their analogs and to assess the effects of modulators in the claimed methods.

(6). Nature of the Invention

The scope of the claims includes many structural variants of constituent peptides of colostrinin and active analogs thereof, but the specification does not provide sufficient teachings on the identities and effects of these peptides in the claimed method. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed methods associated with the variants, and the teachings in the specification are limited, therefore, it is necessary to have additional guidance and to carry out undue experimentation to assess the effects of various constituent peptides of colostrinin and active analogs thereof in the claimed methods.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-7 are indefinite because of the use of the term "combinations thereof" or "4HNE". The term cited renders the claim indefinite, it is not clear what components and how much of each component are included in the combination since the identities of the constituent peptides of colostrinin and/or the active analogs are not indicated in the claim, and what the term

"4HNE" represents. A full spelled out word should be indicated for "4HNE" in the first occurrence. Claims 2-6 are included in the rejection because they are dependent on rejected claims and do not correct the deficiency of the claim from which they depend.

7. Claims 1-7 are indefinite because the claim lacks an essential step in the method of modulating an intracellular signaling molecule or down regulating 4HNE-mediated lipid peroxidation in a cell. The missing step is an effective amount of modulator used (for claims 1-7) and the outcome of the treatment (for claim 7). Claims 2-6 are included in the rejection because they are dependent on rejected claims and do not correct the deficiency of the claim from which they depend.

Conclusion

8. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached at 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner

CHIH-MIN KAM
PATENT EXAMINER

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June 22, 2005